

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

NATERA, INC.,	:	
	:	
Plaintiff,	:	
	:	
v.	:	C.A. No. 20-125-LPS
	:	
ARCHERDX, INC.,	:	
	:	
Defendants.	:	

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MEMORANDUM OPINION

June 28, 2021
Wilmington, Delaware



STARK, U.S. District Judge:

Plaintiff Natera, Inc. (“Natera” or “Plaintiff”) filed suit against Defendant ArcherDX, Inc. (“Archer” or “Defendant”) on January 27, 2020, alleging infringement of U.S. Patent No. 10,538,814 (the “’814 patent”). (D.I. 1) In an amended complaint, which Natera filed on April 15, 2020, Natera further alleged infringement of U.S. Patent Nos. 10,557,172 (the “’172 patent”), 10,590,482 (the “’482 patent”), and 10,597,708 (the “’708 patent”). (D.I. 17) After the Court granted leave (D.I. 115), Natera filed the operative second amended complaint on January 12, 2021, which adds allegations of infringement of U.S. Patent No. 10,731,220 (the “’220 patent”). (D.I. 116)

“The Asserted Patents generally cover specific methods of preparing nucleic acids using the recited steps of nucleic acid amplification of target loci. Some of the Asserted Patent claims further recite performing DNA amplification by PCR using the methodologies in the claims.” (D.I. 177 at 2) (internal citations omitted)

The parties submitted a joint claim construction brief and appendix on April 14, 2021. (D.I. 177, 178) The Court also received technology tutorials and objections to them. (D.I. 129, 130, 148, 149) The Court held a claim construction hearing using videoconference technology on April 26, 2021. (D.I. 185) (“Tr.”)

I. LEGAL STANDARDS

The ultimate question of the proper construction of a patent is a question of law. *See Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 321 (2015) (citing *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 388-91 (1996)). “It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (internal citation and quotation

marks omitted). “[T]here is no magic formula or catechism for conducting claim construction.” *Id.* at 1324.

“[T]he words of a claim are generally given their ordinary and customary meaning. . . . [which is] the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application.” *Id.* at 1312-13 (internal citations and quotation marks omitted). “[T]he ordinary meaning of a claim term is its meaning to the ordinary artisan after reading the entire patent.” *Id.* at 1321 (internal quotation marks omitted). The patent “specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.” *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

While “the claims themselves provide substantial guidance as to the meaning of particular claim terms,” the context of the surrounding words of the claim also must be considered. *Phillips*, 415 F.3d at 1314. Furthermore, “[o]ther claims of the patent in question, both asserted and unasserted, can also be valuable sources of enlightenment . . . [b]ecause claim terms are normally used consistently throughout the patent.” *Id.* (internal citation omitted).

It is likewise true that “[d]ifferences among claims can also be a useful guide. . . . For example, the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim.” *Id.* at 1314-15 (internal citation omitted). This “presumption is especially strong when the limitation in dispute is the only meaningful difference between an independent and dependent claim, and one party is urging that the limitation in the dependent claim should be read into the independent claim.” *SunRace Roots Enter. Co., Ltd. v. SRAM Corp.*, 336 F.3d 1298, 1303 (Fed. Cir. 2003).

It is also possible that “the specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor’s lexicography governs.” *Phillips*, 415 F.3d at 1316. It bears emphasis that “[e]ven when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using words or expressions of manifest exclusion or restriction.” *Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1372 (Fed. Cir. 2014) (internal quotation marks omitted).

In addition to the specification, a court “should also consider the patent’s prosecution history, if it is in evidence.” *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 980 (Fed. Cir. 1995), *aff’d*, 517 U.S. 370 (1996). The prosecution history, which is “intrinsic evidence,” “consists of the complete record of the proceedings before the [Patent and Trademark Office] and includes the prior art cited during the examination of the patent.” *Phillips*, 415 F.3d at 1317. “[T]he prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be.” *Id.*

“In some cases . . . the district court will need to look beyond the patent’s intrinsic evidence and to consult extrinsic evidence in order to understand, for example, the background science or the meaning of a term in the relevant art during the relevant time period.” *Teva*, 574 U.S. at 331. “Extrinsic evidence consists of all evidence external to the patent and prosecution history, including exper. and inventor testimony, dictionaries, and learned treatises.” *Markman*, 52 F.3d at 980. For instance, technical dictionaries can assist the court in determining the meaning of a term to those of skill in the relevant art because such dictionaries “endeavor to collect the accepted meanings of terms used in various fields of science and technology.”

Phillips, 415 F.3d at 1318. In addition, expert testimony can be useful “to ensure that the court’s understanding of the technical aspects of the patent is consistent with that of a person of skill in the art, or to establish that a particular term in the patent or the prior art has a particular meaning in the pertinent field.” *Id.* Nonetheless, courts must not lose sight of the fact that “expert reports and testimony [are] generated at the time of and for the purpose of litigation and thus can suffer from bias that is not present in intrinsic evidence.” *Id.* Overall, while extrinsic evidence “may be useful to the court,” it is “less reliable” than intrinsic evidence, and its consideration “is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence.” *Id.* at 1318-19. Where the intrinsic record unambiguously describes the scope of the patented invention, reliance on any extrinsic evidence is improper. *See Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1308 (Fed. Cir. 1999) (citing *Vitronics*, 90 F.3d at 1583).

Finally, “[t]he construction that stays true to the claim language and most naturally aligns with the patent’s description of the invention will be, in the end, the correct construction.” *Renishaw PLC v. Marposs Societa’ per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998). It follows that “a claim interpretation that would exclude the inventor’s device is rarely the correct interpretation.” *Osram GmbH v. Int’l Trade Comm’n*, 505 F.3d 1351, 1358 (Fed. Cir. 2007) (quoting *Modine Mfg. Co. v. U.S. Int’l Trade Comm’n*, 75 F.3d 1545, 1550 (Fed. Cir. 1996)).

II. CONSTRUCTION OF DISPUTED TERMS

A. “target loci”¹

Plaintiff Segments of nucleic acid of interest
Defendant Regions of interest on the nucleic acid of an individual subject to amplification using primers with sequences complementary to the nucleic acid selected to avoid primer side products
Court Selected segments of nucleic acid of interest of an individual.

The parties agree that “target loci” include regions or segments of interest comprising nucleic acids. (D.I. 177 at 7, 20-21) What remains in dispute is whether those segments are limited to those from a single individual, and whether they must be amplified by complementary-sequenced primers that avoid side products. (*Id.* at 8, 11)

On the first dispute, the Court agrees with Defendant that the segments containing the target loci must be selected from a single individual and may not be segments from multiple individuals. The specification defines “locus” as “a particular region of interest on the DNA (or corresponding RNA) of an individual, which may refer to a SNP, the site of a possible insertion or deletion, or the site of some other relevant genetic variation.” (’220 patent at 34:56-59)² A person of ordinary skill in the art (“POSA”) would understand that a “target locus” incorporates “locus” and the specification’s definition of “locus.” Target loci, being the plural form of target locus, likewise incorporates the definition of locus. Therefore, a POSA would understand that

¹ This term appears in claims 1 and 5-7 of the ’172 patent; claims 1, 7-9, and 17-18 of the ’814 patent; claim 1 of the ’482 patent; claims 1, 6-7, and 16-17 of the ’220 patent; and claims 1 and 9 of the ’708 patent.

² The specification is the same in the ’172, ’814, and ’220 patents. (D.I. 177 at 2) The ’482 and ’708 patents “share some portion of the specification with the other patents.” (*Id.*) For simplicity, the Court sometimes cites to just one of the pertinent specifications.

the multiple target loci would consist of selected segments of nucleic acid of interest “of an individual,” which in this context means from one and only one individual.³

A target is a sequence that includes a polymorphism or other mutation “associated with an increased risk (such as an above normal level of risk) for the disease or phenotype of interest, or associated with the disease or phenotype of interest.” (*Id.* at 10:59-63) Thus, target loci are loci specifically selected because they reveal something about the disease of interest. Even if, therefore, samples can contain target loci from multiple individuals (D.I. 177 at 8-9), the target loci of the claims are only those from one individual for the specific disease or disorder of interest in that individual (*see id.* at 20).

On the second dispute, the Court agrees with Plaintiff that Defendant’s additional language – “subject to amplification using primers with sequences complementary to the nucleic acid selected to avoid primer side products” – is unnecessary. Amplification, primer binding, and avoidance of side products are the subject of other claim limitations. (D.I. 177 at 9-10) Restricting the ambit of “target loci” to only those that “avoid primer side products” would improperly import an additional limitation from the specification in the absence of any indication of a clear intent by the patentee to do so. (*See* D.I. 177 at 22-24)

³ It may be that a single biological sample may contain material from multiple individuals. It may be possible, nonetheless, to practice the claims on such a sample, provided that each time it is practiced all of the target loci are selected from a single individual (i.e., the portion of the sample that is derived from that same single individual). For example, an individual looking to test for Y chromosome linked disorders could obtain a sample of mixed DNA from a mother and a fetus, target DNA of the fetus, and practice the claim with respect to the target loci of that fetus despite the presence of multiple DNA sources in the sample. (Tr. at 27-28) The Court’s construction is not intended to exclude such possibilities.

B. “Nested PCR”⁴

Plaintiff
A subsequent round or rounds of PCR amplification using one or more new primers that bind internally, by at least one base pair, to the primers used in a previous round
Defendant
A subsequent round or rounds of PCR following a previous round of PCR amplification using one or more new primers that bind internally, by at least one base pair, to the primers used in a previous round and that do not extend beyond those primers
Court
A subsequent round or rounds of PCR amplification using one or more new primers that bind internally, by at least one base pair, to the primers used in a previous round

Natera’s proposed construction is taken directly from the specification. (*Compare* D.I. 177 at 27, 32 *with* ’814 patent at 89:50-54) During prosecution, Natera emphasized a certain portion of the specification and highlighted that entire portion in italics – and then highlighted a subpart of that portion with bold *and* italics.⁵ (*See* D.I. 178 Ex. B-12 at 7) ArcherDX argues,

⁴ This term appears in claims 1 and 5 of the ’814 patent; claim 1 of the ’482 patent; and claims 1 and 4 of the ’220 patent.

⁵ The pertinent prosecution history, which is a block quote from the specification with two types of emphasis added during prosecution, reads:

Multiplex PCR may involve a single round of PCR in which all targets are amplified or it may involve one round of PCR followed by one or more rounds of nested PCR or some variant of nested PCR. Nested PCR consists of a subsequent round or rounds of PCR amplification using one or more new primers that bind internally, by at least one base pair, to the primers used in a previous round. Nested PCR reduces the number of spurious amplification targets by amplifying, in subsequent reactions, only those amplification products from the previous one that have the correct internal sequence. Reducing spurious amplification targets improves the number of useful measurements that can be obtained, especially in sequencing. Nested PCR typically entails designing primers completely internal to the previous primer binding sites, necessarily increasing the minimum DNA segment size required for amplification. For samples such as maternal plasma cjDNA, in which the DNA is highly fragmented, the larger assay size reduces the number of distinct cjDNA molecules from which a measurement can be obtained In an embodiment, to offset

unpersuasively, that this addition of emphasis during prosecution – and selective addition of double emphasis to portions of the specification – constitutes a clear and unmistakable disclaimer of other words in the specification, even though those other words appear in both the specification and the pertinent portion of the prosecution history. (*See* D.I. 177 at 30-31; *see also Cordis Corp. v. Medtronic Ave, Inc.*, 511 F.3d 1157, 1177 (Fed. Cir. 2008) (“[A]rgument-based disavowals will be found, however, only if they constitute clear and unmistakable surrenders of subject matter.”)) ArcherDX has identified no court finding a disclaimer in such a scenario and this Court is not persuaded to do so here.

C. “Annealing Step”⁶

Plaintiff
A step in the amplification process to allow one or more primers to hybridize to their complementary sequences
Defendant
The step during amplification prior to a separate extension step in which primers are permitted to hybridize to their complementary sequences
Court
A step in the amplification process to allow one or more primers to hybridize to their complementary sequences

The only dispute “is whether the annealing step is separate from the extension step.” (D.I. 177 at 36) A POSA would generally understand the PCR process as consisting of three steps: denaturing, annealing, and extension. (D.I. 178 Ex. A-1 ¶ 35) In the context of the

this effect, one may use a partial nesting approach where one or both of the second round primers overlap the first binding sites extending internally some number of bases to achieve additional specificity while minimally increasing in the total assay size.

(D.I. 178 Ex. B-12 at 7) (emphasis added by patentee during prosecution history)

⁶ This term appears in claim 15 of the ’814 patent; claim 14 of the ’220 patent; and claim 1 of the ’708 patent.

asserted patents, however, a POSA would understand that the patentee contemplated some overlap, in particular that some extension might occur during the annealing step. (*See, e.g.*, '814 patent at 80:31-39; *see also* D.I. 177 at 35-36 (citing to patents); Tr. at 64 (“The defendants don’t contest that some extension may occur during the annealing step.”)) Defendant’s proposed construction, which would eliminate any allowance for any overlap between annealing and extension, is not consistent with the intrinsic evidence.⁷

D. “Sequencing Tag”⁸

Plaintiffs
A nucleic acid sequence introduced to facilitate sequencing
Defendants
Indefinite
Court
A nucleic acid sequence introduced to carry out the process of high throughput sequencing

Defendant contends that the claim term is indefinite but has failed to demonstrate, by clear and convincing evidence, that a POSA would not understand its bounds with reasonable certainty. As Plaintiff persuasively explains, a sequence introduced to facilitate sequencing is one that “include[s] elements required to carry out the process of high throughput sequencing” (Tr. at 70), such “as are necessary to make the actual sequencing machine operate and functional” (*id.* at 72; *see also* '814 patent at 90:47-64, 95:14-21, 241:19-24) (describing sequences “required by any of the current sequencing platforms” that “enable direct sequencing” or are “necessary for sequencing on a high throughput sequencing platform”).

⁷ Despite the Court’s adoption of Plaintiff’s construction, Defendant will be permitted, at the appropriate time (and if it wishes), to attempt to prove that an accused product does not infringe because, for example, it does not contain a clearly delineated annealing step. Likewise, as this case continues, Defendant will be free to pursue any contention that the claims are invalid because a POSA cannot discern in them a boundary between the annealing step and other steps in the process, such as an extension step. (*See, e.g.*, D.I. 177 at 37-38)

⁸ This term appears in claim 1 of the '814 patent and claim 1 of the '220 patent.

Defendant points to a variety of examples of what could constitute a sequencing tag, such as an Illumina sequencing tag, a sample index, or a barcode. (D.I. 177 at 46-49) And Defendant's expert, Dr. Boehm, opines that "sequencing tag" "may mean many different things depending on the context and what a scientist is seeking to accomplish." (D.I. 178 Ex. B-1 ¶ 45) But he does not opine that a POSA would fail to know how the patents are using the term in the context of the claims; he merely says that the term is used inconsistently in the scientific literature. (*Id.* ¶¶ 35, 38) Defendant has failed, at least at this stage, to provide clear and convincing evidence that the breadth of options for meeting the sequencing tag limitation renders the claim term indefinite. (*See* Tr. at 110) (Plaintiff's counsel explaining that he, too, "can give you a million examples," but POSA would understand in "context of this claim" what matters are "sequences that are enabling the operation of the high throughput sequencing") Defendant will be permitted to attempt to prove its indefinite defense as this case proceeds.

E. "A Melting Temperature of the at Least 2 Primers"⁹

Plaintiffs
<i>Plain and ordinary meaning</i>
Defendants
Indefinite
Court
The temperature at which one-half (50%) of a DNA duplex of each primer and its perfect complement dissociates and becomes single strand DNA.

The '708 patent explicitly defines "a melting temperature" as "the temperature at which one-half (50%) of a DNA duplex of an oligonucleotide (such as a primer) and its perfect complement dissociates and becomes single strand DNA." ('708 patent at 79:28-31) As the

⁹ This term appears in claim 1 of the '708 patent.

prosecution history makes clear, when multiple primers are involved, an annealing temperature¹⁰ that is **greater than** “a melting temperature of the at least 2 primers” is one that is higher than each individual melting temperature of each primer. (D.I. 127 Ex. UU at 6) (distinguishing invention from prior art that “does not teach, suggest or provide any guidance for using higher annealing temperature than the melting temperature of the target specific primers,” noting that “there is no evidence the primers used . . . have a melting temperature equal to or below 55 °C, which is the annealing temperature used”)

Related U.S. Patent No. 9,677,118 (the “’118 patent”) confirms this understanding, as it also shows that the relevant inquiry is whether the “annealing temperature” selected is greater than **each** of the melting temperatures of **each** primer.¹¹ There, a claim to an “annealing temperature for the reaction conditions is greater than a melting temperature of the at least 50 non-identical primers” was distinguished in prosecution as disclosing that “the annealing temperature of an amplification reaction can be higher than the melting temperature of the primers.” (D.I. 127 Ex. II at 6, 11) That is, “a” melting temperature of two or more primers is not one measurement that relates to the whole of all the primers collectively, but instead refers to the specific melting temperature for each of the primers. The Court’s construction is derived from this intrinsic evidence.

¹⁰ The annealing temperature (T_A) is the temperature at which one runs the PCR protocol. (’708 patent at 79:32-33) This annealing temperature must be, “for the reaction conditions . . . greater than a melting temperature of the at least 2 primers.” (*Id.* claim 1) This is because “[a] higher annealing temperature improves the specificity of the PCR amplification and reduces or prevents amplification of non-target loci.” (*Id.* at 45:62-65)

¹¹ The asserted ’708 patent is a continuation of the ’118 patent. “When the application of prosecution disclaimer involves statements from prosecution of a familial patent relating to the same subject matter as the claim language at issue in the patent being construed, those statements in the familial application are relevant in construing the claims at issue.” *Ormco Corp. v. Align Tech., Inc.*, 498 F.3d 1307, 1314 (Fed. Cir. 2007).

Defendant contends the term is indefinite because a POSA would not be able to determine the melting temperature (i.e., the 50% dissociation point) since there are various methods for analysis. (D.I. 177 at 61-67) This is not dispositive. Instead, as Plaintiff points out, the patent contains guideposts for the POSA. For example, the specification expressly discloses two measurement tools: ultraviolet light or Primer3/SantaLucia software. ('708 patent at 81:53-56, 61:38-41) The parties' experts disagree as to whether these different measurement tools (and possibly others) yield significantly different results. (See D.I. 177 at 66, 74) At this stage, the record lacks clear and convincing evidence of indefiniteness.

III. CONCLUSION

The Court will construe the disputed terms as explained above. An appropriate Order follows.